ESC HEART FAILURE
ESC Heart Failure (2021)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13263

ORIGINAL RESEARCH ARTICLE

Palliative care in pulmonary hypertension associated with congenital heart disease: systematic review and expert opinion

Andrew Constantine[1,2], Robin Condliffe[3], Paul Clift[4], Robert Tulloh[5], Konstantinos Dimopoulos[1,2]* and the CHAMPION Steering Committee

[1]*Adult Congenital Heart Centre and Centre for Pulmonary Hypertension, Royal Brompton Hospital, Sydney Street, London, SW3 6NP, UK;* [2]*National Heart and Lung Institute, Imperial College London, London, UK;* [3]*Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield, UK;* [4]*Department of Cardiology, Queen Elizabeth Hospital Birmingham, Birmingham, UK; and* [5]*Bristol Heart Institute, University Hospitals Bristol, Weston NHS Foundation Trust, Bristol, UK*

Abstract

Aims Pulmonary arterial hypertension (PAH) is common amongst patients with congenital heart disease (CHD). It is a severe and complex condition that adversely affects quality of life and prognosis. While quality of life questionnaires are routinely used in clinical pulmonary hypertension practice, little is known on how to interpret their results and manage PAH-CHD patients with evidence of impaired health-related quality of life, especially those with advanced disease and palliative care needs.

Methods and results We performed a systematic review of studies concerning palliative care for people with PAH-CHD, also reviewing the health-related quality of life literature pertaining to these patients. Of 330 papers identified through initial screening, 17 were selected for inclusion. Underutilization of advance care planning and palliative care resources was common. Where palliative care input was sought, this was frequently late in the course of the disease. No studies provided evidence-based clinical criteria for triggering referral to palliative care, a framework for providing tailored care in this patient group, or how to manage the risk of sudden cardiac death and implantable cardioverter defibrillators in advanced PAH-CHD. We synthesize this information into eight important areas, including the impact of PAH-CHD on quality of life, barriers to and benefits of palliative care involvement, advance care planning discussions, and end-of-life care issues in this complex patient group, and provide expert consensus on best practice in this field.

Conclusions This paper presents the results of a systematic review and expert statements on the preferred palliative care strategy for patients with PAH-CHD.

Keywords Congenital heart defects; Pulmonary hypertension; Palliative care; End-of-life care; Advance care planning; Systematic review

Received: 12 October 2020; Revised: 13 January 2021; Accepted: 29 January 2021
**Correspondence to: Konstantinos Dimopoulos, Adult Congenital Heart Centre, Royal Brompton and Harefield NHS Foundation Trust, Sydney Street, London SW3 6NP, UK. Tel: +44 2073528121 ext 82771; Fax: +44 207351 8629. Email: k.dimopoulos02@gmail.com*

Introduction

Pulmonary arterial hypertension (PAH) is prevalent in patients with congenital heart disease (CHD).[1] It is typically the result of a large systemic-to-pulmonary shunt in infancy that has caused pulmonary vascular disease and hence a rise in pulmonary arterial pressures. PAH is associated with increased morbidity and mortality and significantly impacts on patients' health-related quality of life (HR-QoL) for a range of physical and mental domains: reduced physical functioning, symptoms at rest and during exertion, impact on social functioning and employment, side effects from PAH therapies, uncertainty about prognosis, anxiety, and depression.[2–9]

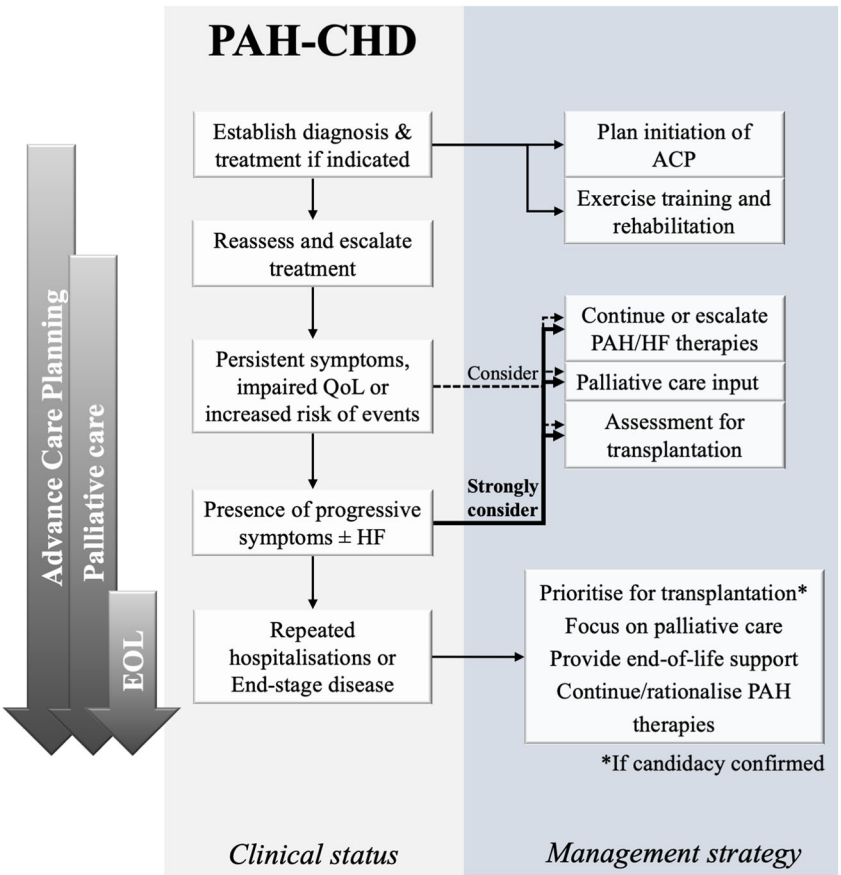
Palliative care provides treatment and support for people with life-limiting illnesses, aimed at improving their HR-QoL and reducing symptom burden for patients and their families.

Palliative care is relevant to patients with PAH related to CHD (PAH-CHD), who may be young but highly symptomatic. To date, there is limited evidence to guide palliative and end-of-life (EOL) care for PAH-CHD patients. International guidelines recommend that physicians should be proactive in discussing advance directives and EOL issues with these patients, along with seeking consultation from palliative care specialists, when appropriate.[10–12]

The unique characteristics of the PAH-CHD population should be recognized when designing palliative care services for these patients (*Figure 1*). These include a wide age range, severe symptom burden, limited therapeutic options, significant morbidity relating to a combination of PAH, CHD, and chronic cyanosis, multiorgan involvement, and comorbidity, including learning difficulties. Physicians looking after these complex patients require high levels of expertise; hence, care is typically provided within highly specialized centres. PAH-CHD physicians should work closely with palliative care teams, identifying the right time to seek palliative care support and facilitate and adhere to palliative care and EOL plans.

We present an expert statement on the role of palliative care in PAH-CHD patients, based on the results of a systematic review of available evidence.

Figure 1 The palliative care framework for patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) should take into account the unique characteristics and natural history of this condition. PAH-CHD can be a rapidly progressive disease, affecting both quality of life (QoL) and prognosis. PAH therapies have now become integral to the management of most patients and are often escalated, aiming at a reduction in morbidity and mortality, and improvement in QoL. Despite this, patients can remain highly symptomatic; the early introduction of advance care planning (ACP) and palliative care can help to alleviate the impact of the disease and agree treatment goals with patients. The onset of congestive heart failure (HF) and/or progression of symptoms should further prompt palliative care involvement in parallel to escalation of PAH therapies (if appropriate) and transplant assessment. The palliative care framework and resources for PAH-CHD patients should reflect the natural history of this disease, integrating components of acquired HF and lung disease care, but accounting for important differences: PAH-CHD is an often-aggressive disease with early onset of symptoms, especially in ES patients, and a high prevalence of multiorgan involvement. Moreover, PAH-CHD patients are younger, with a different impact of the disease on their lives compared with older patients (school/studies/work/sport, etc.).



DOI: 10.1002/ehf2.13263

Methods

The UK-based Congenital Heart disease And pulMonary arterial hyPertension: Improving Outcomes through education and research Networks (CHAMPION) programme has a remit of improving the care of patients with PAH-CHD by supporting clinical decision making, including by identifying gaps in evidence and areas of need in PAH-CHD. We identified palliative care as one such area of need,[13] and this systematic review was used, together with expert opinion, to provide a proposed framework for providing palliative care in the adult PAH-CHD population.

A series of questions around the role and provision of palliative care in PAH-CHD was agreed upon and a systematic review of all published reports related to palliative care in PAH-CHD was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. This was supplemented by a review of the literature on the assessment of HR-QoL in PAH-CHD. Following data synthesis, recommendations were drawn up by the CHAMPION Steering Committee for each section of this review. The systematic review methodology, including search criteria and PRISMA flow-diagram, are detailed in the Supporting information.

Results

Systematic review

Our search identified 330 papers relevant to one or more of the selected topics, of which 263 were excluded after title and abstract screening based on the pre-specified exclusion criteria (supporting information, *Figure S1*). The remaining 67 papers underwent full-text review, of which 50 further papers were excluded. The final group of 17 papers underwent detailed screening for information (*Figure S2*).

Question 1: How does PAH-CHD affect quality of life and which quality of life measures are most meaningful for and applicable to patients with PAH-CHD?

Pulmonary arterial hypertension associated with congenital heart disease can develop at any stage of a patient's life, overlaying one chronic disease on another. Patients with CHD who develop PAH have a poorer exercise tolerance, greater symptom burden, and poorer survival than other CHD patients.[2,3] Altered physical functioning is compounded by impairments in other HR-QoL domains, including psychological and emotional well-being, and social functioning. Generic HR-QoL measures, such as the Medical Outcomes Study Short Form-36 (SF-36), and disease-specific HR-QoL measures, such as the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) and emPHasis-10 questionnaires, have been employed in clinical trials involving PAH-CHD patients (*Table 1*). HR-QoL in patients with PAH-CHD correlates with clinical variables, such as New York Heart Association functional class and 6 -minute walk distance, but not haemodynamic parameters.[4,5] The majority of studies have focussed on patients with Eisenmenger syndrome, in whom the combination of severe pulmonary vascular disease and long-standing cyanosis results in severe exercise intolerance.[6,7] Indeed, exercise performance and HR-QoL is more impaired in Eisenmenger syndrome than in complex cyanotic CHD patients with pulmonary stenosis who have not developed severe pulmonary vascular disease.[8]

Studies of PAH therapies that use HR-QoL as a clinical endpoint are limited to a few small open-label studies, which support the HR-QoL-enhancing effect of PAH therapies.[4,14–20] Nevertheless, HR-QoL has also been shown to be adversely affected by the side effects of PAH therapies, especially continuous prostanoid infusions, and the requirement for frequent hospital contacts needed to monitor therapies in patients with idiopathic PAH[21]; this is also likely to be the case in PAH-CHD. Moreover, almost a quarter of adult patients with Eisenmenger syndrome in contemporary cohorts have Down syndrome, which is associated with learning difficulties, obesity, and sleep apnoea, amongst other comorbidities, all of which impact on HR-QoL and its measurement. Patients with Down syndrome have often been excluded from clinical studies, especially those involving self-rating scales and questionnaires. Unlike other patients with PAH-CHD, HR-QoL improvements have not been shown in this group.[15,16,18,22]

Expert statement The HR-QoL of PAH-CHD patients is affected by a combination of PAH, the congenital heart defect, coexisting syndromes, and other comorbidities, such as learning difficulties. We recommend that HR-QoL measures should be developed and validated specifically for patients with PAH-CHD, to reflect overall life satisfaction, and both physical and mental domains of HR-QoL.[23] Moreover, improving HR-QoL should be a major target for the management of PAH-CHD patients, gathering information from both the patient and their family or caregivers about their physical, psychological, and social well-being, and establishing shared, agreed treatment goals.

Question 2: When should palliative care be introduced and what clinical indications should trigger a palliative care referral in patients with PAH-CHD?

Rather than being an EOL intervention, it is now acknowledged that palliative care should be introduced earlier as an approach to therapy aimed at improving QoL for patients and their families 'through the prevention and relief of suffering by early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial

Table 1 The effect of pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) and its treatment on health-related quality of life (HR-QoL)

First author, year (ref.)	PAH-CHD subtype studied	Subjects *n*	Age inclusion criteria	Age (years)	Intervention	HR-QoL measurement	Time to measurement[a]	Major findings
Observational								
Müller, 2011[8]	ES	58 (35 ES)	≥14 years	27.9 [14–55]	None	SF-36 (g)	Cross-sectional	Impaired HR-QoL in both groups. Worse results in physical and psychosocial domains in ES group
Amedro, 2016[5]	All PAH-CHD	208	≥15 years	42.6 ± 15.8	None	SF-36 (g), CAMPHOR (s), HADS (g)	Cross-sectional	Impaired HR-QoL scores, NYHA functional class, and HADS scores predictive of HR-QoL scores
Favoccia, 2019[64]	All PAH-CHD	314	Adults	51.7 ± 18.4	None	emPHasis-10 (s)	Cross-sectional (2.1 years)	Better HR-QoL in PAH-CHD compared with other forms of PAH. Impaired HR-QoL (higher score) associated with a higher mortality
Exercise								
Martínez-Quintana, 2010[22]	ES	8	Adults	27.7 ± 7.9	Rehabilitation programme	SF-12 (g)	1 year	No significant improvement in HR-QoL
Becker-Grünig, 2013[65]	ES, post-operative PAH-CHD	20	Adults	48 ± 11	Exercise training	SF-36 (g)	15 weeks (2 years)	No significant improvement in HR-QoL
Iron								
Tay, 2011[66]	ES	25 (14 ES)	Adults	39.9 ± 10.9	Intravenous iron therapy	CAMPHOR (s)	3 months	Significant improvement in HR-QoL
ERAs								
Ibrahim, 2006[14]	ES	10	Adults	31.9 ± 10.8	Bosentan	SF-36 (g)	16 weeks (8.1 months)	No significant improvement in HR-QoL
Duffels, 2009[16]	All PAH-CHD	58	Adults	42 [20–75][b]	Bosentan	SF-36 (g), LPH (s)	22 [3–36] months	HR-QoL improvement in non-DS patients only
Duffels, 2009[15]	ES	24	Adults	38 [19–55][b]	Bosentan	SF-36 (g)	11.5 [3–23] months	No significant improvement in HR-QoL
Blok, 2015[17]	All PAH-CHD	61[c]	Adults	42 ± 14	Bosentan	SF-36 (g)	4.5 [0.3–6.4] years	Decrease in SF-36 PCS following initiation of PAH therapy predicted mortality
Vis, 2013[18]	ES	64	Adults	41.3 ± 15.6	Bosentan	SF-36 (g)	4 years	Improvement in 2/8 domains in non-DS patients only to 3 years
PDE5 inhibitors								
Tay, 2011[19]	ES	12	≥16 years	34.3 ± 10.2	Sildenafil	CAMPHOR (s)	3 months	Significant improvement in HR-QoL (all domains)
Clavé, 2019[20]	ES, significant left–right shunt	31	≥10 years	28 [10–54]	Sildenafil, tadalafil	SF-36 (g)	6 months	Significant improvement in HR-QoL

(*Continues*)

Table 1 (continued)

First author, year (ref.)	PAH-CHD subtype studied	Subjects *n*	Age inclusion criteria	Age (years)	Intervention	HR-QoL measurement	Time to measurement[a]	Major findings
Prostanoids								
Soo Cha, 2013[4]	ES	13	Adults >20 years	45 ± 11	Iloprost	SF-12 (g)	24 weeks	Significant improvement in HR-QoL, which correlated with 6MWD, but not changes in haemodynamic parameters

6MWD, 6 min walk distance; CAMPHOR, Cambridge Pulmonary Hypertension Outcome Review; DS, Down syndrome; ERA, endothelin receptor antagonist; ES, Eisenmenger syndrome; g, generic; HADS, Hospital Anxiety and Depression Scale; LPH; (Minnesota) Living with Pulmonary Hypertension questionnaire; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PCS, physical component summary; PDE-5, phosphodiesterase-5; s, disease-specific; SF-12/36, Medical Outcomes Study Short Form-12/36.
[a]Total study period also reported in brackets if different.
[b]Age was reported by Duffels *et al*. as mean [range].
[c]Thirty-nine subjects included in analysis at longest follow-up time.

and spiritual'.[24] In oncology, early involvement of palliative care improves overall HR-QoL and mood.[25]

Our systematic review indicates that palliative care input is often sought late in the course of disease of patients with PAH and CHD.[26–29] Even though the majority of surveyed patients with CHD (with complex or simple lesions) prefer to be informed about their disease course before they face life-threatening complications, even patients with advanced or complex disease may not be offered palliative care at the right time, or at all.[30–32] The systematic review identified putative clinical indications for palliative care input in patients with PAH and/or CHD, linked to management issues that were either commonly encountered, less well-managed by the primary team or where prognosis was guarded. For example, Swetz *et al*. assessed the HR-QoL of PAH patients and found that many patients had a 'profound and multifactorial symptom burden' that adversely impacted HR-QoL and sometimes persisted even with optimal PAH therapy.[26] Despite this, few (<5%) patients were receiving palliative care or pain management input. Another study identified two areas of clinical management that the vast majority of physicians involved in the clinical care of patients with PAH were not 'very comfortable' managing, namely, HR-QoL and issues around pain. Hence, patients who have been identified as having a lower HR-QoL or pain complex management needs, for example, requiring opioids, antidepressants, or other neuromodulators, could be highlighted for palliative care involvement.[27] Apart from symptom management, other issues addressed at initial palliative care consultation may inform the timing and indications of palliative care referrals. In a study of children with advanced heart disease, including CHD, palliative care input tackled goals of care, provision of psychological support, and advance care planning (ACP).[28] Finally, in infants with complex CHD, for example, hypoplastic left heart syndrome, where there is still a high initial mortality, almost one half of congenital cardiothoracic surgeons were in favour of palliative care referral at prenatal diagnosis.[29]

Unfortunately, despite these studies pointing to possible indications for palliative care referral in PAH and in children with CHD, the systematic review identified no studies that identify robust clinical criteria, which should trigger referral for palliative care in patients with PAH-CHD.

Expert statement A 'parallel planning' approach to palliative care is recommended for patients with PAH-CHD, with palliative care referral and assessment performed early, alongside active multidisciplinary management and treatment with PAH therapies (*Figure 1*).[33] There is little evidence to guide the timing of palliative care referral in this population in terms of clinical indications. Markers of advanced disease, such as the initiation of parenteral PAH therapy or referral for transplant assessment, should certainly trigger a referral to palliative care. However, this may be late for a patient

group who are often highly symptomatic at diagnosis and who might not be candidates for these two treatment options. Transition to adult care is a key moment for discussing future treatments and prognosis, and the availability and potential benefits of concurrent palliative care input should be discussed at this point.

Question 3: Who should initiate discussions about the role of palliative care and advance care planning? How should these discussions be broached?

The systematic review identified two studies where it was noted that most patients prefer ACP and palliative care discussions and information to come from their specialist compared with another cardiologist or their primary care provider.[31,34] The majority of patients were willing to speak to a palliative care specialist, although none of the studies directly compared patient preferences regarding the involvement of palliative care in ACP, in addition to or place of the specialist care provider. The privileged position of PAH-CHD specialists, providing long-term, often lifelong, care for their patients, allows a strong rapport and a sense of collaborative decision making to be formed over time. This was reflected by several studies reporting the willingness of most patients to discuss future goals, plans, and expectations with their specialist physician earlier in the disease course, including information about the average life expectancy for patients with their heart condition and EOL issues.[31,32,35,36]

To achieve this, PAH-CHD specialists need to be supported with adequate resources and training, including advanced communication skills, to initiate ACP conversations. In one survey of adult CHD care providers, the vast majority (87%) were interested in communication strategies for ACP discussions, with almost as many (79%) reporting that it would be helpful to have more information and resources on the subject. Kovacs *et al*. have produced recommendations to enhance conversations around ACP in adult CHD patients.[37] There is an emphasis on sufficient time, space, and privacy for these important discussions, hence scheduling a specific visit to discuss goals of care and EOL care. Introducing such conversations as 'routine discussions' that are made 'with all patients' helps to normalize them. Open questions must be used to discover what patients understand about their condition and are willing to talk about, as well as to confirm that they comprehend the issues discussed. Such discussions are complex and often require more than one visit to complete. Once agreed, careful documentation of the patient's wishes is key.

Expert statement Palliative care discussions should be initiated by PAH-CHD specialists, seeking help from palliative care specialists. The communication style and the topics covered should be individualized, tailored to the age of the patient, their underlying condition, and the coexistence of mental health problems or learning difficulties. End-stage patients who have greater palliative care needs should be managed in joint multidisciplinary clinics in specialist PAH-CHD centres, offering support from clinical nurse specialists, CHD specialist physicians with an interest in advanced disease, palliative care specialists, social workers, family support, and pastoral care workers. For this approach to be successful, healthcare providers should receive education and training on the role of palliative care early in their career, which continues during their training.

Question 4: What are the barriers to palliative care involvement in the PAH-CHD population?

The systematic review identified several studies that address potential obstacles to palliative care involvement, summarized as patient-related, physician-related or healthcare-related (*Figure 2*).[13,26,27,29,31,32,34,36] Misconceptions by patients, families, and healthcare practitioners of the role of palliative care are common. It is often presented by professionals as equivalent to EOL care and, thus, synonymous with 'giving up', or being incompatible with active life-prolonging PAH treatments.[27,29] Difficulties in defining the prognosis for patients with PAH-CHD, for example, adults with Eisenmenger syndrome, were also identified as a major barrier.[26]

Even when CHD physicians believe that they discuss life expectancy, ACP, and resuscitation preferences with their patients routinely, their perceptions of performance are very different to those of their patients. Tobler *et al*. found that 50% of providers, but only 1% of patients, surveyed indicated that they had discussed EOL planning,[31] even though the majority (76%) of patients stated they were ready to discuss ACP, regardless of the severity of their underlying CHD.[36]

Organizational barriers to effective palliative care have not been studied but are also a major barrier. In the UK, a survey conducted by the CHAMPION group found that 81% of responders felt there was a lack of formal palliative care services for PAH-CHD patients. Recommendations for changes in practice have been formulated for patients with CHD, as well as those with advanced lung disease or acquired heart failure.[33,37–40]

Expert statement Several barriers still exist resulting in the underutilization of palliative care resources for PAH-CHD. Lines of communication with specialist palliative care teams need to be strengthened to align goal setting, information sharing, and decision making between teams. This calls for a palliative care presence at PAH-CHD clinical multidisciplinary meetings, where management strategies are discussed, as well as joint consultations between PAH-CHD and palliative care specialists in clinics attended by patients with advanced disease.

A shared care framework can improve palliative care provision without placing unreasonable demands on existing resources. Such a model has been proposed by Moynihan

Figure 2 Barriers to effective palliative care involvement, involving different stakeholders of PAH-CHD care, and recommendations for adapting care towards successful integration and provision of palliative care. [+]Misconceptions surrounding palliative care include the belief that palliative care is equivalent to end-of-life or hospice care, that is, it equates to 'giving up' or 'losing hope', is incompatible with active PAH therapy and is exclusively the remit of palliative care specialists. ACP, advanced care planning; EOL, end-of-life; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PC, palliative care.

	Stakeholders of PAH-CHD Care		
	Patient	**Health Care Professional**	**Health System**
Barriers to palliative care involvement	• Self-perception of symptoms / disease severity • Misconceptions of PC+ • Fear, denial or questions about relevance • Lack of awareness of available PC resources • Emotional distress, anxiety and depression	• Prognostic uncertainty • Focus on life-prolonging measures • Misconceptions of PC+ • Lack of formal training in ACP/EOL discussions • Discomfort with tackling quality of life issues • Greater distress in providing EOL care in the young • Inexperience with prescribing PC medication	• Lack of co-ordination of an individual's PC • Lack of specialist PC services for PAH-CHD • Inaccessibility to wider PC resources • Lack of integration with community-based teams • Clinical time constraints • Lack of detailed guidelines and outcome data on PC in PAH-CHD
Adaptations for better care	• Update/inform patients of prognosis, potential for uncertainty • Discuss goals of care • Address patient expectations • Educate about help available • Empower patient decision making • Manage emotional distress / improve mental health	• Do not use prognostication as sole driver to guide therapy • Routinely assess and optimize quality of life • Engage with professional education and training • Create curricula for physicians with a special interest in PC • Communication training • Clear documentation of ACPs • Psychological and bereavement support for providers • Seek specialist PC team input in complex issues • Create a culture of open communication and shared decision making	• Identify a named PAH-CHD specialist to co-ordinate care for each patient • Establish strong links/work jointly with PC teams with an interest in PAH-CHD • Educate and promote the resources available in the wider PC team • Build links to community-based EOL care • Create "protected" spaces for ACP/EOL discussions • Develop guidelines for PC in PAH-CHD • Promote audit and research to improve the evidence base for PC in PAH-CHD

et al. for use in paediatric cardiac intensive care units,[41] which can easily be applied to the adult PAH-CHD service. The model relies on the selection and training of interdisciplinary palliative care 'champions'. This group of healthcare professionals should include psychologists, senior nurse practitioners, cardiologists, cardiac intensivists, surgeons, and allied health professionals, who receive additional palliative care training through courses and subspecialty rotations. In turn, this group of professionals strengthens palliative care provision through training of other staff, creating palliative care pathways, and developing quality improvement initiatives. They should liaise between PAH-CHD, palliative care, and interdisciplinary support staff on an individual basis depending on case complexity and specific needs. This type of model can extend the reach of palliative care using current numbers of palliative care specialists, through local education, training, and empowerment.

At the same time, education for patients, families, healthcare providers, and also policy makers is key to overcome barriers to palliative care by addressing common misconceptions of palliative care and empowering shared goal setting and decision making. The process of educating ourselves and our patients cannot be purely opportunistic, relying on the 'right moment' arising in clinic. Rather, structured education at clinic appointments designed for this purpose, through patient groups and using digital platforms and new technologies is necessary. For healthcare professionals looking after patients with PAH-CHD, clear pathways for how and when to access palliative care resources (tailored to the local resources available at each trust) should be available. They should be coupled with communication training and opportunities for further professional education for those with a special interest in palliative care. This should be strengthened at a national and international level by clear guidelines for palliative care in PAH-CHD and promotion of quality improvement and research to improve the evidence base for palliative care provision in this population.

Question 5: What are the potential benefits and treatment targets for patients and their families of palliative care involvement?

The importance of palliative care in chronic illness, including in PAH and acquired heart failure, has been highlighted in several reviews, and benefits include minimizing symptoms and burdensome therapies while maximizing HR-QoL, psychological well-being, independence, and social functioning.[33] In acquired heart failure patients, the effect of palliative care interventions was studied recently in the PAL-HF trial. Patients were randomized to conventional heart failure management alone or with integrated, interdisciplinary palliative care. The latter afforded a benefit in heart-failure-related and overall HR-QoL parameters.[42] Yet, there remains a paucity of clinical studies testing the impact of palliative care interventions in PAH and PAH-CHD. Our review yielded only one study designed to test a palliative care intervention in all-comers attending heart failure and transplant clinic, including patients with CHD. In this quality-improvement project, training in ACP discussions increased the rate of documented ACP discussions from 0% to 75% over the 2 year study period.[43]

Regardless, patients and their families often have clear ideas about their objectives when palliative care is involved. In a study of children with advanced heart disease receiving palliative care review, including patients with CHD, two-thirds of families stated that their primary goal was for their child to live as long and as comfortably as possible. Improved survival with comfort is compatible with the concept of 'parallel planning'. Children whose families stated that comfort was their primary goal at EOL were less likely to die in an intensive care unit, and more likely to die in a comfort care setting, with no life-sustaining treatment.[28]

Expert statement The benefits of timely, integrated palliative care involvement go beyond symptom relief, providing physical, psychological and social support for patients with serious illness and their families or caregivers (*Figure 3*). Moreover, palliative care aims to improve the HR-QoL of all those affected by the condition, both patients and their families. Despite the paucity of data measuring the benefits of palliative care in PAH-CHD, palliative care has the potential to improve the lives of patients and their families, especially when care is provided in a framework where palliative care can be effectively integrated with specialist medical care.

Figure 3 Multidimensional facets and goals of palliative care involvement. QoL, quality of life.

DOI: 10.1002/ehf2.13263

Question 6: Should there be a different framework for providing palliative care to PAH-CHD patients, compared with other services?

In the absence of specialized palliative care services for PAH-CHD, patients often have to fit into acquired heart failure or chronic obstructive pulmonary disease services. This does not allow the creation of a tailored service, nor does it serve the unique features of the PAH-CHD population, who are typically young, often diagnosed prenatally with CHD, and may have complex comorbidities relating to pulmonary hypertension, residual haemodynamic defects, long-standing cyanosis, and other syndromes. There are differences in symptom prevalence and severity between PAH and other disorders where palliative input is often sought, with a higher prevalence of exertional dyspnoea, fatigue, and palpitations than similar studies in patients receiving cancer therapy.[44] The EOL experiences of PAH-CHD patients are also likely to differ from other patient groups. For example, compared with patients with cancer, adults with CHD were more likely to have an inpatient or intensive care admission in the last 30 days of life.[45] Similarly, children with CHD were likely to die during withdrawal of life-sustaining interventions (78%), with parents realizing that their child had no realistic chance of survival a median of 2 days before death.[46] For PAH-CHD patients, who have often received care from the same congenital heart team since birth, it can be difficult, if not inappropriate, to 'transition patient care to another group of providers as EOL approaches'.[47]

Expert statement Palliative and EOL care services that target the specific needs of PAH-CHD patients are desirable.[13] Hence, a PAH-CHD palliative care framework should (i) be able to cater for patients of all ages, (ii) combine elements of cardiac and respiratory palliative care, and (iii) integrate fully into current PAH-CHD care. Care goals, expectations, and service delivery need to be aligned between specialities and be appropriate for the age and level of maturity of the individual patient (*Figure 1*). The transition period, between paediatric and adult services, can be seen as a 'key moment' for identifying ideal candidates for palliative care input, initiating a discussion about expectations and ACP.[40]

Palliative care services for PAH-CHD patients should integrate components of palliative care designed for advanced lung disease or heart failure.[39] Pulmonary rehabilitation and the creation of individualized action plans can help improve the management of dyspnoea crises, with learning from cardiac palliative care on the management of patients with congestive heart failure. Lessons can be learned also from both lung and cardiac palliative care with regard to polypharmacy and coping with multiple therapies with significant side effects, the impact of transplantation listing and/or long-term mechanical circulatory support and decisions regarding EOL and withdrawal of treatments.[48]

A lead doctor and named nurse should be chosen to oversee EOL care for each patient,[49] but close partnership with palliative care specialists with an interest in chronic cardiopulmonary disease and life-limiting disease affecting younger patients is imperative to allow the best possible use of palliative care resources. We can draw from the experience of specialities who look after young patients with lifelong respiratory diseases,[50] such as cystic fibrosis, where a speciality-led palliative care model is used, in which the specialist cystic fibrosis team meet the majority of the palliative care needs of their patients, following established pathways and guidelines, and refer to palliative care specialists in complex cases when additional support is needed.[51]

Question 7: What can palliative care offer towards the end of life? What is the role of advance decisions and DNACPR orders in this group?

ACP is the process by which a patient's wishes and EOL care preferences are discussed and agreed upon. Early, effective communication practices around goals of therapy and the risk of complications can set the stage for subsequent, more involved conversations about prognosis, patients' wishes and preferences. Steiner *et al*. found that adult CHD inpatients had a significantly greater resource utilization, with a higher rate of hospital and intensive care unit admissions towards the EOL compared with patients with cancer or acquired heart failure.[45] The same study found that adult CHD patients were more likely to have an ACP in place than cancer patients, although the systematic review identified variable rates of ACP depending on the setting and cohort. However, in the outpatient setting, ACP is much less frequent. In another study on adults with CHD, EOL discussions had occurred in only 6% of patients prior to their terminal admission. Even during the terminal admission, the majority of discussions took place late in the hospital stay, at a median of 2 days before death. At this point, conversations are much more likely to focus on de-escalation of therapy than patients' wishes and HR-QoL enhancement.[52] Moreover, this close to death, many patients lose capacity and conversations are more likely to be had with the family and carers. Tobler *et al*. previously reported on a group of hospitalized adults with CHD; immediately prior to death, 44% of patients were receiving mechanical ventilation, while over half (52%) died under attempted resuscitation.[52] The systematic review did not identify any studies exploring the associated question of whether specific invasive therapies where discussed as part of ACP and how often ACP decisions were followed at the point of an acute deterioration.

Pulmonary arterial hypertension patients who suffer from cardiac arrest rarely survive, making successful cardiopulmonary resuscitation very unlikely. Hence, Do Not Attempt Cardiopulmonary Resuscitation (DNACPR) discussions will be appropriate for patients with advanced disease and should, ideally, be anticipatory, undertaken by senior physicians,

sensitive to the wishes and concerns of the patient and their family, and in the wider context of ACP.[53]

Expert statement Well-timed, sensitive, open communication with patients and their families is essential. Discussions have to take into account the patient's age, level of understanding, and emotional readiness to take on information about prognosis, treatment goals, resuscitation, and plans for EOL care. Patients must be made aware of EOL services and palliative care options. Patient preferences and wishes about their future care should be documented clearly in their notes and can be recorded formally as advance decisions to refuse treatment (*Table 2*). For patients who do not wish to make an advance decisions to refuse treatment, 'advance statements' can be helpful, allowing patients to organize their thoughts about their wishes and preferences around any aspect of their future care. In order to be useful, patient preferences should be specific and reflect the choices they are likely to be faced with if their clinical status deteriorates in-hospital or at home, acknowledging that many patients who deteriorate acutely in hospital may become too unwell to be discharged to their preferred place of death. This requires clinicians to provide patients with adequate information, in an honest and easy to understand manner, which allows them to make their choices. Only a minority of patients will not be ready for such conversations or prefer not to talk about the terminal phase of their illness. In such cases, it is important to highlight the need for planning and suggest that patients might select a family member, carer, or friend to assist them, or they may wish to appoint a lasting power of attorney to make decisions for them, should they lose capacity. Ideally, the clinical team should communicate directly with the patients when they have capacity and should ascertain their wishes well before they lose capacity. Only when patients do not have capacity to make decisions should family members or carers be approached as the primary point of contact.

A DNACPR order should be discussed with PAH-CHD patients with advanced disease on maximal therapy with a guarded prognosis, who are not on a transplant list.

Question 8: How should the risk of sudden cardiac death be managed in PAH-CHD? What is the role of implantable cardioverter defibrillators in this cohort?

Sudden cardiac death is not uncommon in patients with CHD, including those with PAH.[54] Previous studies identifying predictors of mortality in PAH-CHD have not focused on sudden arrhythmic events.[55–57] A recent retrospective study of patients with Eisenmenger syndrome has identified predictors of sudden cardiac death in this subgroup, but identifying patients in the wider PAH-CHD population who may benefit from automated implantable cardioverter defibrillator (ICD) implantation as primary prevention remains less than straightforward.[58] Moreover, the decision to proceed to ICD implantation, even in secondary prevention, needs to be individualized, to account for age, functional status, life expectancy, and the expected mode of death, that is, arrhythmic sudden cardiac death versus progressive ventricular dysfunction or respiratory failure. Finally, ICD implantation can be associated with complications, including a high risk of lead-related complications of up to 25% over 10 years, infective endocarditis, inappropriate shocks, and the need for anticoagulation in patients with large intracardiac

Table 2 Advance care planning and the methods by which plans for future care can be set

Methods of instructing future care	Description
Advance care planning	A process that supports adults at any age or stage of health in understanding and sharing their personal values, life goals, and preferences regarding future medical care. The goal is to ensure that people receive medical care that is consistent with their values, goals, and preferences during serious and chronic illness.[a]
Advance statement	A written and signed statement, which sets out the patient's preferences, wishes, beliefs, and values regarding their future care. This may include any aspect of care, including the location of care, preferences, and religious or spiritual beliefs.
Advance decision (living will or advance decision to refuse treatment)	A legally binding document regarding a decision to refuse a named treatment (including life-sustaining treatment) in a specific circumstance in the future.
Lasting power of attorney (LPA) for Health and Welfare	The legal appointment of a personal welfare attorney who can make health and welfare decisions on behalf of a person, when their capacity to make such decisions is lost. If specified, this can include decisions about life-sustaining treatments.
Do Not Attempt CPR (DNACPR) decision	An anticipatory order, completed on a standardized form and shared between healthcare professionals, which can provide immediate guidance on the best action to take (or not take) should the person suffer a cardiac arrest. The decision can be made in advance by a capacitous patient who wishes to refuse CPR, or as a result of high-quality, timely communication by a doctor with a patient and their surrogate (unless the patient has requested confidentiality or only the surrogate where the person lacks capacity) based on the futility of CPR or the balance of benefits/burdens of CPR.[b]

CPR, cardiopulmonary resuscitation.
[a]The International Consensus Definition of Advance Care Planning.[67]
[b]Modified from the guideline document from the British Medical Association, Resuscitation Council (UK) and the Royal College of Nursing.[53]

communications.[59–61] Even in congenital cardiac conditions where risk factors for sudden cardiac death have been identified (e.g. tetralogy of Fallot), the mortality benefit of ICDs is yet to be demonstrated.[11]

Expert statement The role of ICDs for primary or secondary prevention remains unclear in PAH and a question for future research. When contemplating ICD implantation, physicians should consider the patient's life expectancy (ideally >1 year), their functional class (to be avoided in those in functional Class IV who are not candidates for transplantation), and individualized risks of device complications and anticoagulation.[62] Hence, ICD insertion may not be appropriate for many patients with advanced PAH-CHD. For patients who have an ICD and are approaching the later stages of their disease, discussions about ICD deactivation should form part of ACP. These concepts should ideally be discussed at the time of ICD implantation. In patients nearing EOL, ICD deactivation should be part of the DNACPR discussion, when attempts at CPR are considered inappropriate and HR-QoL is the primary aim.[63]

Discussion

Early adoption of palliative care practices in patients with PAH-CHD, including HR-QoL assessment and ACP, promotes a holistic approach to care, which optimizes physical and emotional well-being. Palliative care should be part of the training of all PAH-CHD providers, who should address the palliative care needs of their patients in close collaboration with palliative care specialists. A multidisciplinary approach to palliative care for PAH-CHD patients can target intractable symptoms and address complex issues, discordant patient–family goals, and unrealistic expectations of prognosis or treatment effects.[40] Integrating palliative care strategies into the ongoing, active management of PAH-CHD patients challenges the concept of palliative care as an EOL intervention. Instead, it allows the provision of continuous, high-quality parallel planning during the gradual shift from life-prolonging therapy towards palliation.

In this review, we provide expert opinion on important topics relating to palliative care in PAH-CHD, based on the findings of a systematic review of published studies. Palliative care remains an underutilized resource in this population, and barriers to effective palliative care adoption and utilization still need to be overcome. Education of existing healthcare providers and empowerment of patients through an open dialogue is key to capitalize on available resources. Frequent discussions about current milestones and future goals, with appropriately timed ACP conversations, encourage timely shared decision making. PAH-CHD specialists need to be aware of available palliative care resources and must be able to perform parallel planning when escalating PAH therapies, considering referral to transplantation, preventing and aggressively treating complications that may arise, but should also ensure that their treatment choices do not weigh heavily on the QoL of the patient.

Ultimately, this young, highly complex patient group does not fit the mould of many other disease groups requiring palliative care input, and existing palliative care pathways and guidelines should be combined and refined, based on our understanding of the pathophysiology and management of PAH-CHD, in order to optimize patient care from a prognostic and HR-QoL point of view.

Study limitations

This body of work has important limitations, primarily related to the limited evidence in terms of the number of papers and quality of evidence on HR-QoL measures and palliative care interventions in this group of patients. The primary scope of the search was to inform expert opinion rather than to provide a completely evidence-based recommendation. There is urgent need for research in this area, as demonstrated by the scarcity of evidence on this important clinical topic.

Conclusions

Pulmonary arterial hypertension associated with congenital heart disease is a life-limiting condition with a high symptom burden and reduced HR-QoL. Improving palliative care provision in this complex group of patients involves better education, treatment coordination, and direction of resources. Palliative care should be a collaborative effort between PAH-CHD experts and palliative care specialists, provided in centres with adequate expertise in the management of both PAH and CHD. The paucity of studies on HR-QoL and palliative care in PAH-CHD calls urgently for multicentre collaboration and hypothesis-driven research to further guide clinical practice.

Acknowledgements

We would like to acknowledge Professor Karen Forbes, Consultant in Palliative Care, University Hospitals Bristol and Weston NHS Foundation Trust for her valuable comments on our manuscript. Medical writing support for this manuscript was provided by nspm ltd., Meggen, Switzerland. Eleanor Hobbs (nspm ltd.) acted as an independent reviewer for the systematic review.

Conflict of interest

All authors have been consultants to and have received grant support and personal fees from Janssen-Cilag Limited during the conduct of the study. Dr Condliffe has received personal fees from Bayer and GlaxoSmithKline. Dr Clift has received personal fees from Bayer. Professor Tulloh has received personal fees from Pfizer, Abbott International, GlaxoSmithKline, and Bayer. Professor Dimopoulos has received grants and personal fees from Pfizer, GlaxoSmithKline, and Bayer/MSD.

Funding

The manuscript was funded by Janssen-Cilag Limited, who had no influence on manuscript writing.

Author contributions

All authors contributed to the conception and design of the work as the CHAMPION steering committee. A.C. and K.D. performed the systematic review, data extraction, and interpretation. A.C. drafted the manuscript with input from all authors. K.D., R.C., P.C. and R.T. critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Sources of support

Medical writing support for this manuscript was provided by nspm ltd, Meggen, Switzerland and funded by Janssen-Cilag Limited, who had no influence on manuscript writing.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Systematic review inclusion and exclusion criteria.
Figure S2. Flow diagram showing the stages involved in choosing eligible publications for the systematic review (modified from the PRISMA recommendations).

References

1. Duffels MGJ, Engelfriet PM, Berger RMF, van Loon RLE, Hoendermis E, Vriend JWJ, van der Velde ET, Bresser P, Mulder BJM. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. *Int J Cardiol* 2007; **120**: 198–204.
2. Engelfriet PM, Duffels MGJ, Möller T, Boersma E, Tijssen JGP, Thaulow E, Gatzoulis MA, Mulder BJM. Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. *Heart* 2007; **93**: 682–687.
3. Lowe BS, Therrien J, Ionescu-Ittu R, Pilote L, Martucci G, Marelli AJ. Diagnosis of pulmonary hypertension in the congenital heart disease adult population impact on outcomes. *J Am Coll Cardiol* 2011; **58**: 538–546.
4. Cha KS, Cho KI, Seo JS, Choi JH, Park YH, Yang DH, Hong GR, Kim DS. Effects of inhaled iloprost on exercise capacity, quality of life, and cardiac function in patients with pulmonary arterial hypertension secondary to congenital heart disease (the Eisenmenger syndrome) (from the EIGER Study). *Am J Cardiol* 2013; **112**: 1834–1839.
5. Amedro P, Basquin A, Gressin V, Clerson P, Jais X, Thambo JB, Guerin P, Cohen S, Bonnet D. Health-related quality of life of patients with pulmonary arterial hypertension associated with CHD: the multicentre cross-sectional ACHILLE study. *Cardiol Young* 2016; **26**: 1250–1259.
6. Diller G-P, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation* 2005; **112**: 828–835.
7. Dimopoulos K, Okonko DO, Diller G-P, Broberg CS, Salukhe TV, Babu-Narayan SV, Li W, Uebing A, Bayne S, Wensel R, Piepoli MF, Poole-Wilson PA, Francis DP, Gatzoulis MA. Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. *Circulation* 2006; **113**: 2796–2802.
8. Müller J, Hess J, Hager A. Exercise performance and quality of life is more impaired in Eisenmenger syndrome than in complex cyanotic congenital heart disease with pulmonary stenosis. *Int J Cardiol* 2011; **150**: 177–181.
9. Lewis R, Armstrong I, Bergbaum C, Brewis MJ, Cannon J, Charalampopoulos A, Church AC, Coghlan JG, Davies RJ, Dimopoulos K, Elliot C, Gibbs JSR, Gin-Sing W, Haji G, Hameed AG, Howard LS, Johnson MK, Kempny A, Kiely DG, Giudice FL, McCabe C, Peacock AJ, Peleyeju O, Pepke-Zaba J, Polwarth G, Price L, Sabroe I, Schreiber BE, Sheares K, Taboada D, Thompson AAR, Toshner MR, Wanjiku I, Wort SJ, Yorke J, Condliffe R. EmPHasis-10 health-related quality of life score predicts outcomes in patients with idiopathic and connective tissue disease-associated pulmonary arterial hypertension: results from a UK multi-centre study. *Eur Respir J* 2020. https://doi.org/10.1183/13993003.00124-2020
10. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M.

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015; **46**: 903–975.
11. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, Crumb SR, Dearani JA, Fuller S, Gurvitz M, Khairy P, Landzberg MJ, Saidi A, Valente AM, van Hare G. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019; **139**: e698–e800.
12. Baumgartner H, Bonhoeffer P, De Groot NMS, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJM, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E, Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC), Association for European Paediatric Cardiology (AEPC), ESC Committee for Practice Guidelines (CPG). ESC guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010; **31**: 2915–2957.
13. Tulloh R, Dimopoulos K, Condliffe R, Clift P. Management of adults with congenital heart disease and pulmonary arterial hypertension in the UK: survey of current practice, unmet needs and expert commentary. *Heart Lung Circ* 2018; **27**: 1018–1027.
14. Ibrahim R, Granton JT, Mehta S. An open-label, multicentre pilot study of bosentan in pulmonary arterial hypertension related to congenital heart disease. *Can Respir J* 2006; **13**: 415–420.
15. Duffels MGJ, Vis JC, van Loon RLE, Berger RMF, Hoendermis ES, van Dijk APJ, Bouma BJ, Mulder BJM. Down patients with Eisenmenger syndrome: is bosentan treatment an option? *Int J Cardiol* 2009; **134**: 378–383.
16. Duffels MGJ, Vis JC, van Loon RLE, Nieuwkerk PT, van Dijk APJ, Hoendermis ES, de Bruin-Bon RHACM, Bouma BJ, Bresser P, Berger RMF, Mulder BJM. Effect of bosentan on exercise capacity and quality of life in adults with pulmonary arterial hypertension associated with congenital heart disease with and without Down's syndrome. *Am J Cardiol* 2009; **103**: 1309–1315.
17. Blok IM, van Riel ACMJ, Schuuring MJ, Duffels MG, Vis JC, van Dijk APJ, Hoendermis ES, Mulder BJM, Bouma BJ. Decrease in quality of life predicts mortality in adult patients with pulmonary arterial hypertension due to congenital heart disease. *Neth Heart J* 2015; **23**: 278–284.
18. Vis JC, Duffels MG, Mulder P, de Bruin-Bon RHACM, Bouma BJ, Berger RMF, Hoendermis ES, van Dijk APJ, Mulder BJM. Prolonged beneficial effect of bosentan treatment and 4-year survival rates in adult patients with pulmonary arterial hypertension associated with congenital heart disease. *Int J Cardiol* 2013; **164**: 64–69.
19. Tay ELW, Papaphylactou M, Diller GP, Alonso-Gonzalez R, Inuzuka R, Giannakoulas G, Harries C, Wort SJ, Swan L, Dimopoulos K, Gatzoulis MA. Quality of life and functional capacity can be improved in patients with Eisenmenger syndrome with oral sildenafil therapy. *Int J Cardiol* 2011; **149**: 372–376.
20. Clavé MM, Maeda NY, Thomaz AM, Bydlowski SP, Lopes AA. Phosphodiesterase type 5 inhibitors improve microvascular dysfunction markers in pulmonary arterial hypertension associated with congenital heart disease. *Congenit Heart Dis* 2019; **14**: 246–255.
21. Rival G, Lacasse Y, Martin S, Bonnet S, Provencher S. Effect of pulmonary arterial hypertension-specific therapies on health-related quality of life: a systematic review. *Chest* 2014; **146**: 686–708.
22. Martínez-Quintana E, Miranda-Calderín G, Ugarte-Lopetegui A, Rodríguez-González F. Rehabilitation program in adult congenital heart disease patients with pulmonary hypertension. *Congenit Heart Dis* 2010; **5**: 44–50.
23. Moons P, Van Deyk K, Budts W, De Geest S. Caliber of quality-of-life assessments in congenital heart disease: a plea for more conceptual and methodological rigor. *Arch Pediatr Adolesc Med* 2004; **158**: 1062–1069.
24. WHO|WHO Definition of Palliative Care. WHO, https://www.who.int/cancer/palliative/definition/en/ (accessed 25 May 2020).
25. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF, Billings JA, Lynch TJ. Early palliative care for patients with metastatic non–small-cell lung cancer. *N Engl J Med* 2010; **363**: 733–742.
26. Swetz KM, Shanafelt TD, Drozdowicz LB, Sloan JA, Novotny PJ, Durst LA, Frantz RP, McGoon MD. Symptom burden, quality of life, and attitudes toward palliative care in patients with pulmonary arterial hypertension: results from a cross-sectional patient survey. *J Heart Lung Transplant* 2012; **31**: 1102–1108.
27. Fenstad ER, Shanafelt TD, Sloan JA, Novotny PJ, Durst LA, Frantz RP, McGoon MD, Swetz KM. Physician attitudes toward palliative care for patients with pulmonary arterial hypertension: results of a cross-sectional survey. *Pulm Circ* 2014; **4**: 504–510.
28. Marcus KL, Balkin EM, Al-Sayegh H, Guslits E, Blume ED, Ma C, Wolfe J. Patterns and outcomes of care in children with advanced heart disease receiving palliative care consultation. *J Pain Symptom Manage* 2018; **55**: 351–358.
29. Morell E, Thompson J, Rajagopal S, Blume ED, May R. Congenital cardiothoracic surgeons and palliative care: a national survey study. *J Palliat Care* 2019; **36**: 17–21.
30. Grinnan D, Swetz K, Pinson J, Lyckholm L, Smith T. The end-of-life experience of a cohort of patients with pulmonary arterial hypertension. *J Pain Symptom Manage* 2012; **43**: 445–446.
31. Tobler D, Greutmann M, Colman JM, Greutmann-Yantiri M, Librach LS, Kovacs AH. End-of-life in adults with congenital heart disease: a call for early communication. *Int J Cardiol* 2012; **155**: 383–387.
32. Tobler D, Greutmann M, Colman JM, Greutmann-Yantiri M, Librach SL, Kovacs AH. Knowledge of and preference for advance care planning by adults with congenital heart disease. *Am J Cardiol* 2012; **109**: 1797–1800.
33. Khirfan G, Tonelli AR, Ramsey J, Sahay S. Palliative care in pulmonary arterial hypertension: an underutilised treatment. *Eur Respir Rev* 2018; **27**: 180069.
34. Steiner JM, Stout K, Soine L, Kirkpatrick JN, Curtis JR. Perspectives on advance care planning and palliative care among adults with congenital heart disease. *Congenit Heart Dis* 2019; **14**: 403–409.
35. Deng LX, Gleason LP, Khan AM, Drajpuch D, Fuller S, Goldberg LA, Mascio CE, Partington SL, Tobin L, Kim YY, Kovacs AH. Advance care planning in adults with congenital heart disease: a patient priority. *Int J Cardiol* 2017; **231**: 105–109.
36. Greutmann M, Tobler D, Colman JM, Greutmann-Yantiri M, Librach SL, Kovacs AH. Facilitators of and barriers to advance care planning in adult congenital heart disease. *Congenit Heart Dis* 2013; **8**: 281–288.
37. Kovacs AH, Landzberg MJ, Goodlin SJ. Advance care planning and end-of-life management of adult patients with congenital heart disease. *World J Pediatr Congenit Heart Surg* 2013; **4**: 62–69.
38. Kirkpatrick JN, Kim YY, Kaufman BD. Ethics priorities in adult congenital heart disease. *Prog Cardiovasc Dis* 2012; **55**: 266–273.e3.
39. Khateeb D, West F. Palliative management and end-of-life care in nonmalignant advanced lung disease. *Clin Pulm Med* 2017; **24**: 206–214.
40. Troost E, Roggen L, Goossens E, Moons P, de Meester P, van de Bruaene A, Budts W. Advanced care planning in adult congenital heart disease: transitioning from repair to palliation and end-of-life care. *Int J Cardiol* 2019; **279**: 57–61.
41. Moynihan KM, Snaman JM, Kaye EC, Morrison WE, DeWitt AG, Sacks LD, Thompson JL, Hwang JM, Bailey V,

Lafond DA, Wolfe J, Blume ED. Integration of pediatric palliative care into cardiac intensive care: a champion-based model. *Pediatrics*; **144**. Epub ahead of print 2019: e20190160.
42. Rogers JG, Patel CB, Mentz RJ, Granger BB, Steinhauser KE, Fiuzat M, Adams PA, Speck A, Johnson KS, Krishnamoorthy A, Yang H, Anstrom KJ, Dodson GC, Taylor DH Jr, Kirchner JL, Mark DB, O'Connor CM, Tulsky JA. Palliative care in heart failure: the PAL-HF randomized, controlled clinical trial. *J Am Coll Cardiol* 2017; **70**: 331–341.
43. Edwards LA, Bui C, Cabrera AG, Jarrell JA. Improving outpatient advance care planning for adults with congenital or pediatric heart disease followed in a pediatric heart failure and transplant clinic. *Congenit Heart Dis* 2018; **13**: 362–368.
44. Matura LA, McDonough A, Carroll DL. Symptom prevalence, symptom severity, and health-related quality of life among young, middle, and older adults with pulmonary arterial hypertension. *Am J Hosp Palliat Care* 2014; **33**: 214–221.
45. Steiner JM, Kirkpatrick JN, Heckbert SR, Sibley J, Fausto JA, Engelberg RA, Randall Curtis J. Hospital resource utilization and presence of advance directives at the end of life for adults with congenital heart disease. *Congenit Heart Dis* 2018; **13**: 721–727.
46. Blume ED, Balkin EM, Aiyagari R, Ziniel S, Beke DM, Thiagarajan R, Taylor L, Kulik T, Pituch K, Wolfe J. Parental perspectives on suffering and quality of life at end-of-life in children with advanced heart disease: an exploratory study*. *Pediatr Crit Care Med* 2014; **15**: 336–342.
47. Crossland DS, Van De Bruaene A, Silversides CK, Hickey EJ, Roche SL. Heart failure in adult congenital heart disease: from advanced therapies to end-of-life care. *Can J Cardiol* 2019; **35**: 1723–1739.
48. Sobanski PZ, Alt-Epping B, Currow DC, Goodlin SJ, Grodzicki T, Hogg K, Janssen DJA, Johnson MJ, Krajnik M, Leget C, Martínez-Sellés M, Moroni M, Mueller PS, Ryder M, Simon ST, Stowe E, Larkin PJ. Palliative care for people living with heart failure: European Association for Palliative Care Task Force expert position statement. *Cardiovasc Res* 2020; **116**: 12–27.
49. NHS Proposed Congenital Heart Disease Standards and Service specifications - NHS England - Citizen Space, https://www.engage.england.nhs.uk/consultation/congenital-heart-disease-standards/ (accessed 31 May 2020).
50. Bowater SE, Speakman JK, Thorne SA. End-of-life care in adults with congenital heart disease: now is the time to act. *Curr Opin Support Palliat Care* 2013; **7**: 8–13.
51. Bourke SJ, Doe SJ, Gascoigne AD, Heslop K, Fields M, Reynolds D, Mannix K. An integrated model of provision of palliative care to patients with cystic fibrosis. *Palliat Med* 2009; **23**: 512–517.
52. Tobler D, Greutmann M, Colman JM, Greutmann-Yantiri M, Librach LS, Kovacs AH. End-of-life care in hospitalized adults with complex congenital heart disease: care delayed, care denied. *Palliat Med* 2012; **26**: 72–79.
53. Guidance from the British Medical Association, the Resuscitation Council (UK) and the Royal College of Nursing. Decisions relating to cardiopulmonary resuscitation, https://www.resus.org.uk/EasySiteWeb/GatewayLink.aspx?alId=16643 (2016, accessed 31 May 2020).
54. Daliento L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G, Stone S. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J* 1998; **19**: 1845–1855.
55. Kempny A, Hjortshøj CS, Gu H, Li W, Opotowsky AR, Landzberg MJ, Jensen AS, Søndergaard L, Estensen ME, Thilén U, Budts W, Mulder BJ, Blok I, Tomkiewicz-Pająk L, Szostek K, D'Alto M, Scognamiglio G, Prokšelj K, Diller GP, Dimopoulos K, Wort SJ, Gatzoulis MA. Predictors of death in contemporary adult patients with Eisenmenger syndrome: a multicenter study. *Circulation* 2017; **135**: 1432–1440.
56. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. *Eur Heart J* 2014; **35**: 716–724.
57. Diller G-P, Dimopoulos K, Broberg CS, Kaya MG, Naghotra US, Uebing A, Harries C, Goktekin O, Gibbs JS, Gatzoulis MA. Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study. *Eur Heart J* 2006; **27**: 1737–1742.
58. Chiriac A, Riley DC, Russell M, Moore JP, Padmanabhan D, Hodge DO, Spiegel MR, Vargas ER, Phillips SD, Ammash NM, Madhavan M. Determinants of sudden cardiac death in adult patients with Eisenmenger syndrome. *J Am Heart Assoc* 2020; **9**: e014554.
59. Khairy P, Landzberg MJ, Gatzoulis MA, Mercier LA, Fernandes SM, Côté JM, Lavoie JP, Fournier A, Guerra PG, Frogoudaki A, Walsh EP, Dore A, Epicardial Versus ENdocardial pacing and Thromboembolic events Investigators. Transvenous pacing leads and systemic thromboemboli in patients with intracardiac shunts: a multicenter study. *Circulation* 2006; **113**: 2391–2397.
60. Koneru JN, Jones PW, Hammill EF, Wold N, Ellenbogen KA. Risk factors and temporal trends of complications associated with transvenous implantable cardiac defibrillator leads. *J Am Heart Assoc* 2018; **7**: e007691.
61. Özcan C, Raunsø J, Lamberts M, Køber L, Lindhardt TB, Bruun NE, Laursen ML, Torp-Pedersen C, Gislason GH, Hansen ML. Infective endocarditis and risk of death after cardiac implantable electronic device implantation: a nationwide cohort study. *Europace* 2017; **19**: 1007–1014.
62. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
63. Jaarsma T, Beattie JM, Ryder M, Rutten FH, McDonagh T, Mohacsi P, Murray SA, Grodzicki T, Bergh I, Metra M, Ekman I, Angermann C, Leventhal M, Pitsis A, Anker SD, Gavazzi A, Ponikowski P, Dickstein K, Delacretaz E, Blue L, Strasser F, McMurray J, on behalf of the Advanced Heart Failure Study Group of the HFA of the ESC. Palliative care in heart failure: a position statement from the palliative care workshop of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2009; **11**: 433–443.
64. Favoccia C, Kempny A, Yorke J, Armstrong I, Price LC, McCabe C, Harries C, Wort SJ, Dimopoulos K. EmPHasis-10 score for the assessment of quality of life in various types of pulmonary hypertension and its relation to outcome. *Eur J Prev Cardiol* 2019; **26**: 1338–1340.
65. Becker-Grünig T, Klose H, Ehlken N, Lichtblau M, Nagel C, Fischer C, Gorenflo M, Tiede H, Schranz D, Hager A, Kaemmerer H, Miera O, Ulrich S, Speich R, Uiker S, Grünig E. Efficacy of exercise training in pulmonary arterial hypertension associated with congenital heart disease. *Int J Cardiol* 2013; **168**: 375–381.
66. Tay ELW, Peset A, Papaphylactou M, Inuzuka R, Alonso-Gonzalez R, Giannakoulas G, Tzifa A, Goletto S, Broberg C, Dimopoulos K, Gatzoulis MA. Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome. *Int J Cardiol* 2011; **151**: 307–312.
67. Sudore RL, Lum HD, You JJ, Hanson LC, Meier DE, Pantilat SZ, Matlock DD, Rietjens JAC, Korfage IJ, Ritchie CS, Kutner JS, Teno JM, Thomas J, McMahan RD, Heyland DK. Defining advance care planning for adults: a consensus definition from a multidisciplinary Delphi panel. *J Pain Symptom Manage* 2017; **53**: 821–832.e1.